REMARKS

Claim Amendment

Claims 1 and 8 have been amended to recite methods of using replicon and helper RNAs to produce packaged alphavirus particles, wherein the replicon contains a sequence encoding a nonstructural protein nsp2 that contains a leucine, glycine or valine mutations or proline at amino acid position 726. Support for these recited mutations can be found on page 29, lines 3-8; page 32, lines 2-9; and Figure 10.

Claims 1 and 8 has also been amended to recite the claimed methods comprise the steps of obtaining a primary stock of viral particles after transfection, and obtaining a secondary larger stock of viral particles after infecting a second group of cells, wherein the secondary stock has a titer of at least 1 x 10^8 infectious units/ml. The present specification teaches that high titer of packaged viral particles can be maintained in tissue culture by infecting cells at high multiplicity of infection (page 21, lines 7-11; page 37, lines 1-3; and page 40, lines 17-18).

Claim 2 has been amended to recite the claimed method further comprises a step of infecting a third group of cells with the

secondary stock of viral particles, and obtaining viral particles with a titer of at least 1 x 10^8 infectious units/ml. Support for the amended claim can be found on page 18, lines 18-20, which teaches titers of packaged replicons approached 3-5x10^8 inf.u./ml after electroporation and 1-2x10^9 inf.u./ml after passage 1, 2 and 3 (see also Tables 1 and 2).

Claims 15 and 17 are added to recite the Sindbis virus replicon used in the present invention comprises a structural RNA element that increases RNA translation efficiency. Support for the claims can be found on page 26, line 15 to page 28, line 12.

Claims 16 and 18 are added to recite the structural RNA element is a G-C rich sequence located 28 nucleotides downstream from an initiating AUG of Sindbis virus subgenomic RNA. Support for the claims can be found on page 27, lines 2-4 and lines 13-18.

Drawings

Figures 13 and 14 are objected to for misspelling "Helper" as "Helperr". Applicant hereby submits replacement drawing sheets incorporating the corrected spelling.

Claim Objection

Claims 1, 6 and 13 are objected to for some informalities. The examiner stated that claim 1 is missing the word "a" on line 20 before the term "secondary stock", and claims 6 and 13 are missing the word "the" before the term "replicational enhancer". Claims 1, 6 and 13 have been amended as suggested by the examiner.

Rejections Under 35 USC §112, 2nd Paragraph

Claims 1-14 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The rejection is respectfully traversed.

The Examiner rejected claims 1, 2 and 8 for reciting the term "high titer(s)". The Examiner stated that except for claims 7 and 14, which limit the low point of the titer, the specification provides no description of what values constitute a "high titer". Applicant submits that claims 1, 2 and 8 have been amended to delete the phrase "high titer(s)" and recite a minimum value for the titer.

Claim 8 was rejected for reciting the term "large scale production". The Examiner stated that the specification provides no description on what might constitute "large scale production".

Applicant submits that claim 8 has been amended to remove the rejected phrase.

Applicant submits that the claims as amended have particularly pointed out and distinctly claimed the subject matter of the invention. Accordingly, applicant respectfully requests that the rejection of claims 1-14 under 35 U.S.C. §112, second paragraph, be withdrawn.

35 USC §112, 1st Paragraph Rejections

Claim 2 is rejected under 35 U.S.C. §112, first paragraph, for failing to comply with written description requirement. The rejection is respectfully traversed.

The Examiner states that the invention is drawn to a method of producing alphavirus particles by infecting a group of cells with an alphavirus stock prepared from the same group of cells. The Examiner contends the claims read on a very large genus of potential alphaviruses and cell types, yet the specification only discloses Sindbis virus with two nsP2 mutations (P726G and P726V) can be serially reproduced on BHK-21 cells. The Examiner contends that applicant claims re-infection of cells by alphaviruses by function only without a correlation between structure and function, and the prior

art does not compensate for the lack of description of specific examples of alphavirus mutants suitable as claimed.

Applicant submits that independent claim 1 has been amended to recite using Sindbis virus replicon encoding a nonstructural protein nsp2 that contains a proline, leucine, glycine or valine at amino acid position 726. The specification discloses Sindbis virus replicons having a proline to leucine, proline to glycine or proline to valine mutations at amino acid 726 all have reduced cytopathic effects (page 29, lines 3-8; page 32, lines 2-9; and Figure 10). Hence, applicant submits that in view of the prior art and the instant disclosure, one of ordinary skill in the art would readily recognize that the recited Sindbis virus replicon mutants could be used in the claimed method and be serially reproduced in cells such as BHK-21 cells.

Applicant submits that the claim as amended contains subject matter which was sufficiently described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Accordingly, applicant respectfully requests that the rejection of claim 2 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claim 2 is rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

The Examiner states the test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. The Examiner indicates that the reference of Frolov et al. identified Sindbis virus mutants at position 726 in the nsP2 protein display a wide range of RNA replication efficiencies and cytopathic effects. Given this data, the examiner contends that it is unpredictable that mutations at this single residue can lead to a Sindbis virus phenotype capable of serial replication in a mammalian cell.

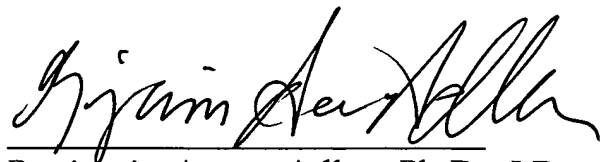
As discussed above, independent claim 1 has been amended to recite using Sindbis virus replicon encoding a nonstructural protein nsp2 that contains a proline, leucine, glycine or valine at amino acid position 726. The instant specification discloses Sindbis viruses with these mutations all have reduced cytopathic effects (page 29, lines 3-13; page 32, lines 2-9). Applicant submits that in view of the disclosures in the application, one skilled in the art would readily recognize that Sindbis virus replicons having a proline to leucine, proline to glycine or proline to valine mutations at

amino acid 726 would all have phenotypes capable of serial replication in commonly used mammalian cells due to reduced cytopathic effects. Hence, one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. Accordingly, applicant requests that the rejection of claim 2 under 35 U.S.C. §112, first paragraph, be withdrawn.

This is intended to be a complete response to the Office Action mailed November 17, 2004. If any issues remain outstanding, the examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: Jan 12, 2005



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